COMPARATIVE STUDY OF EFFICACY OF HAND FOOT PSORALEN ULTRAVIOLET A THERAPY VERSUS SEQUENTIAL THERAPY OF TOPICAL CLOBETASOL PROPIONATE WITH TOPICAL CALCIPOTRIOL OINTMENT IN PALMOPLANTAR PSORIASIS

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

in partial fulfillment of the requirements for the award of

M.D. DEGREE (BRANCH-XII)

IN

DERMATOLOGY, VENEREOLOGY AND LEPROLOGY

APRIL 2013

CERTIFICATE

This is to certify that the dissertation entitled **"Comparative study of efficacy of hand foot psoralen ultraviolet A therapy versus sequential therapy of topical clobetasol propionate with topical calcipotriol ointment in palmoplantar psoriasis"** is the bonafide original work of Dr.P.Abirami in partial fulfillment of the requirements for MD DERMATOLOGY, VENEREOLOGY AND LEPROLOGY BRANCH XII examination of the Tamilnadu DR.M.G.R Medical University, Chennai to be held in April 2013. The period of study was from December 2011 to November 2012.

Date :

Professor and Head of the Department,

Department of Dermatology,

Coimbatore Medical College and Hospital,

Coimbatore.

Date :

Dean,

Coimbatore Medical College and Hospital,

Coimbatore.

Coimbatore Medical College

COIMBATORE, TAMILNADU, INDIA - 641 014

(Affiliated to The Tamilnadu Dr. MGR Medical University, Chennai)

ETHICS COMMITTEE

CERTIFICATE

Name of the Candidate : DR. P. ABIRAMI

Course : M.D. DERMATOLOGY, VENEREOLOGY & LEPROLOGY

Period of Study : SEPTEMBER 2011 - NOVEMBER 2012

College : COIMBATORE MEDICAL COLLEGE

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IN PALMOPLANTAR PSORIASIS
THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY
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COMPARATIVE STUDY OF EFFICACY OF HAND FOOT PSORALEN ULTRAVIOLET A THERAPY VERSUS SEQUENTIAL THERAPY OF TOPICAL CLOBETASOL PROPIONATE WITH TOPICAL CALCIPOTRIOL OINTMENT IN PALMOPLANTAR PSORIASIS Dissertation submitted to THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY in partial fulfillment of the requirements for the award of M.D. DEGREE (BRANCH-XII) IN DERMATOLOGY, VENEREOLOGY AND LEPROLOGY APRIL 2013 CERTIFICATE This is to certify that the dissertation entitled "Comparative study of efficacy of hand foot psoralen ultraviolet A therapy versus sequential therapy of topical clobetasol propionate with topical calcipotriol ointment in palmoplantar psoriasis" is the bonafide original work of...

DECLARATION

I Dr.P.Abirami solemnely declare that the dissertation entitled **"Comparative study of efficacy of hand foot psoralen ultraviolet A therapy versus sequential therapy of topical clobetasol propionate with topical calcipotriol ointment in palmoplantar psoriasis"** is a bonafide work done by me at Coimbatore Medical College Hospital during the year December 2011 to November 2012 under the guidance and supervision of Dr.P.P.Ramasamy M.D.,D.D., Professor and Head of Department, Department of Dermatology, Coimbatore Medical College Hospital.

The dissertation is submitted to Dr.MGR Medical University towards partial fulfillment of requirement for the award of MD degree branch XII Dermatology, Venereology and Leprology.

PLACE:

DATE: **Dr.P.ABIRAMI**

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ABSTRACT

TITLE : COMPARATIVE STUDY OF EFFICACY OF HAND FOOT PSORALEN ULTRAVIOLET A THERAPY VERSUS SEQUENTIAL THERAPY OF TOPICAL CLOBETASOL PROPIONATE WITH TOPICAL CALCIPOTRIOL OINTMENT IN PALMOPLANTAR PSORIASIS

BACKGROUND

Psoriasis is a common genetically determined chronic inflammatory skin disease. It is characterized by well defined erythematous plaque with silvery white scales. It is commonly distributed over the elbow, knee, lower back, nails, scalp, palms and soles. It is associated with varying periods of remission and relapse. Various modalities of treatment have been tried. The main goal of therapy is rapid control of the disease and to maintain a longer duration of remission. Treatment of palmoplantar psoriasis and remission maintenance is very difficult.

AIM OF THE STUDY

The aim of the study is to compare the efficacy of topical psoralen and ultraviolet A phototherapy with sequential therapy of topical 0.05% clobetasol propionate ointment and topical 0.005% calcipotriol ointment in palmoplantar

psoriasis and to observe the adverse effects, remission maintenance and PASI percentage reduction of more than 50% in both groups.

MATERIALS AND METHODS

50 patients are included in the study. The population for the study included patients attending outpatient Department of Dermatology, Coimbatore Medical College Hospital, Coimbatore. The patients are divided into two groups, group A and group B. The treatment duration was 6 months and the follow up period was 6 months. Each group has 25 patients.

Group A patients received topical hand foot PUVA therapy with minimum dose of 1J/cm2 with increment dosage of 0.5J/cm2, in the frequency two times per week and the maximum dose of 24.5J/cm2 in some patients. Eyes were protected by using goggles during treatment.

In group B sequential therapy of calcipotriol ointment combinations given in three phases, in phase 1 combination of clobetasol propionate and calcipotriol ointment once a day application in the first month, in phase 2 clobetasol propionate for weekends and calcipotriol for week days once a day application in the second and third month, in phase 3 calcipotriol ointment once a day application in the fourth, fifth and sixth month. PASI score and PASI percentage reduction was assessed at the end of 8^{th},16^{th},24^{th} weeks.

RESULTS

During treatment, 3 patients in group A and 1 patient in group B lost follow up. In both groups none of the patients showed complete clearance of both palms and plantar lesions.

In group A out of 22 patients, 20 (90%) showed more than 50% reduction of PASI score. Four patients showed complete clearance of lesion in the palms. Two patients showed complete clearance of lesion in the soles. The average period of clearance of lesions was at 19 weeks. In six months follow up period 3 patients showed relapse after 15 weeks of average period of remission. 4 patients showed adverse effect like erythema and burning sensation. In group B out of 24 patients, all (100%) showed more than 50% reduction of PASI score. Seven patients showed complete clearance of lesion in the palms and five patients showed complete clearance of lesion in the soles. The average period of clearance of lesions was at 20.3 weeks. In six months follow up period 2 patients showed relapse after 20 weeks of average period of remission. 3 patients showed adverse effect like erythema,itching and burning sensation.

CONCLUSION

The efficacy of topical calcipotriol ointment and steroid used in sequential manner is better than the topical psoralen ultraviolet A therapy. All the patients (100%) in calcipotriol and steroid combination group showed more than 50% reduction of PASI score. But in PUVA therapy group 90% of patients showed more than 50% reduction of PASI score. On comparing the adverse effects, patients on PUVA therapy group developed more adverse effects than the patients on calcipotriol and steroid combination group. The duration of remission maintenance was long in calcipotriol and steroid combination group when compared to PUVA therapy group.

In our study, we arrived at the conclusion that topical therapies used in a sequential manner was more effective and it may be considered as a first line therapy for the treatment of patients with palmoplantar psoriasis.

KEY WORDS: Hand Foot PUVA, calcipotriol – clobetasol combinations, PASI score and percentage reduction

INTRODUCTION

Psoriasis is a common genetically determined chronic inflammatory skin disease. It is characterized by well defined erythematous plaque with silvery white scales. It is commonly distributed over the elbow, knee, lower back, nails, scalp, palms and soles. It is associated with varying periods of remission and relapse. Various modalities of treatment have been tried. The main goal of therapy is rapid control of the disease and to maintain a longer duration of remission.

AIMS AND OBJECTIVES

1. To compare the efficacy of topical psoralen and ultraviolet A phototherapy with sequential therapy of topical 0.05% clobetasol propionate ointment and topical 0.005% calcipotriol ointment in palmoplantar psoriasis.
2. To observe the reduction in percentage of PASI (psoriasis area and severity index) score above 50% in both groups.
3. To observe the adverse effects of both treatment modalities.
4. To observe the duration of remission after treatment, during the study period.

REVIEW OF LITERATURE

HISTORY

The Greeks divided skin disease into 3 categories of psora, lepra, leichen. Lepra derived from greek word lopos (epidermis) and lepo (scale). 'Lepra' includes psoriasis, vitiligo, alopecia areata, boils, and eczema [1]. The bibilical term 'tsaraat' or 'zaraath' includes leprosy & psoriasis. Hippocrates and his school classified dry scaly eruptions as 'lopoi' which included psoriasis and leprosy. The first recognizable clinical description of psoriasis is credited to Roman sage Aureliues Cornelius Celsus (25 BC-45AD) [2]. 'Psora' means desquamation or itch and it was first used by Galen (133-200AD). He described psoriasis as a pruritic scaly skin disease of the eyelids and scrotum. Robert Willan gave accurate description of psoriasis in 1809, but he did not differentiate it from leprosy. He also described it as 'lepra vulgaris'. Ferdinand Von Hebra differentiated psoriasis and leprosy clinically in 1841. Heinrich Koebner first described Koebner phenomenon.

EPIDEMIOLOGY

The prevalence of psoriasis in the world is 0.1-3%. The incidence is 60/100000 per year. In India 0.44% to 2.8% populations are affected by psoriasis[3]. The incidence is increased in first and second degree relatives. Males and females are equally affected in psoriasis. A study from North India, Bedi et al reported male to female ratio is 2.5:1 [4].

GENETIC FACTORS

Psoriasis is commonly associated with HLA Cw6 other associations include HLA-B 13, HLA-B 17, HLA-B 37, HLA-B 16, HLA- B27 and the Chromosome is 6. It is divided into two types according to HLA association and age [5]. Type 1 is associated with HLA Cw6 with family history and severe manifestations. The age of onset is at 20-30 years. Type 2 is non HLA cw6 associated with absence of family history and mild manifestations. The age of onset is 50-60 years. Concordance for psoriasis is more common with monozygotic twins. Familial occurrence of the disease is 7-36%. Rarely it is associated with autoimmune diseases like vitiligo and bullous pemphigoid.

TRIGGERING FACTORS

1. Trauma: Psoriatic lesions will develop at the site of trauma in the skin. This is called as Koebner phenomenon.
2. Smoking and alcohol will also exacerbate the disease.
3. Stress: It will exacerbate or trigger the disease in 60% of the patients.
4. Exacerbation during winter season.
5. Pregnancy: In pregnancy remission may occur due to increase level of IL-10 in the circulation and in postpartum period disease will be exacerbated.
6. Infections: Infections like streptococci and HIV will exacerbate the disease.
7. Drugs: Drugs will precipitate or exacerbate the disease. The drugs include lithium salts, NSAIDs, anti malarials, ACE inhibitors, β adrenergic blocking agents and high dose estrogen therapy.

PATHOGENESIS

Psoriasis has been regarded as a T cell-driven disease for the past two decades [6, 7].Psoriasis is caused by abnormalities in the adaptive immune system and in the innate immune function of resident epidermal cells [8]. Recently it is considered as an inflammatory epithelial disease [9].

IMMUNOPATHOGENESIS

Epidermis contains CD8 T cells and dermis contains mixture of both CD4 and CD8 T cells. The T cells are memory cells and natural killer cells (NK cells). Memory T cells are the majority cells, which express cutaneous lymphocyte associated antigen (CLA) which act as skin homing receptor and chemokine receptor CCR4. NK cells interact with CD1d on keratinocytes. So it increases the production of IFN gamma which contributes to additional immune mechanism. Increased activity of Langerhans cells and dendritic cells cause potent immunostimulatory capacity. Increased dermal and epidermal dendrocytes activate T cells. Plasmocytoid dendritic cells initiate psoriasis by production of IFN gamma [10].

Although the activated neutrophils contribute to pathogenesis, they are not considered to be the primary cause of psoriasis. Angiogenesis is increased due to overexpression of vascular endothelial growth factors like E-selectin and ICAM on dermal vessels in lesional skin. So it leads to accumulation of T lymphocytes.

CYTOKINES AND CHEMOKINES

Increased level of Th1 cytokines mainly IFN gamma and IL-2, decreased level of anti inflammatory cytokines IL-10 and increased production of IL-12, IL-23, and IL-15 contibute to the disease. IL-23 stimulates Th cells to release IL-22. This mechanism causes keratinocyte overproliferation and dermal inflammation.

INNATE IMMUNITY

Innate immune cytokines are upregulated due to overactivity of dendritic cells, NK cells, neutrophils and epidermal keratinocytes.

DIFFERENT CLINICAL TYPES OF PSORIASIS

1. Chronic plaque psoriasis
2. Guttate psoriasis
3. Arthropathic psoriasis
4. Pustular psoriasis
5. Erythrodermic psoriasis
6. Unstable psoriasis
7. Regional variations in psoriasis

    Scalp

    Nails

    Palms and sole

Face

Flexures

Scrotum

Napkin area

8. Special variants

   Rupioid

   Elephantine

   Ostraceous psoriasis

9. Atypical variants [11, 12] – seborrhoeic psoriasis, mucosal lesions, ocular lesions, linear and zonal lesions, digital and interdigital, verrucous lesions, follicular form and lichenoid variety.

PALMOPLANTAR PSORIASIS

Palmoplantar psoriasis that accounts for 3% - 4% of all psoriasis cases produces significant functional and social disability [13]. Reduction of pain and improvement in the function of limbs are more important therapeutic goals than complete clearance. Psoriasis in the soles will present as discrete scaly plaques, diffuse hyperkeratotic plaques or erythematous plaques. Sometimes fissures may be present. Nowadays, psoriasis is considered as a heterogeneous disease and many authors define palmoplantar pustulosis as a separate clinical entity with its genetic

predisposition, course, and therapeutic management which differ from psoriasis itself [14].

CLINICAL VARIANTS OF PALMOPLANTAR PSORIASIS ACCORDING TO NOBEL CLASSIFICATION [19]

1. Sharply demarcated erythematous patches and covered by adherent psoriatic scales.
2. Diffuse mild hyperkeratosis with scales.
3. Very thick hyperkeratotic layer resembling hereditary type of palmoplantar keratoderma
4. Diffuse erythema.

NOBEL CATEGORIZATION OF PALMOPLANTAR PSORIASIS [19]

Mild - Noble type 1 and 2

Moderate - Noble type 3

Severe - Noble type 4

DIFFERENTIAL DIAGNOSIS

1. Chronic allergic contact dermatitis
2. Tinea pedis
3. Palmoplantar keratoderma
4. Porokeratosis

PASI score

It was first described in 1978. The severity of psoriasis is assessed by psoriasis area severity index. According to Carlin et al PASI score reduction of 50% corresponds to a clinically significant endpoint in assessment of palmoplantar psoriasis [15-18].

INVESTIGATIONS

Psoriasis is usually diagnosed clinically but rarely requires biopsy for confirmation.

The histopathological findings are

Hyperkeratosis

Parakeratosis

Munromicro abscess in the stratum corneum

Thin or absent granular layer

Supra papillary thinning (part of stratum malphigii) with presence of spongiform pustule of Kogoj.

Regular elongation of rete ridges and thickening of their lower portion showing club shape (camel foot appearance).

Dilated tortuous capillaries in the papillae and perivascular infiltration of mononuclear cells.

TREATMENT OF PALMOPLANTAR PSORIASIS

In 19th century arsenic and ammoniated mercury were used to treat psoriasis [20-23]. Reassurance and emotional support is needed before starting treatment. Avoidance of aggravating factors is the first step in the management.

Topical therapy is the first line of treatment. Systemic therapy is advised if the disease is refractory to topical therapy.

MULTI-MODALITY THERAPEUTIC STRATEGIES

a) Combination therapy: To reduce toxicity, the two therapeutic agents are given simultaneously. After attaining therapeutic response the accelerator is tapered and maintenance agent is continued.

b) Rotational therapy [24]: To prevent cumulative effect, the drugs are given rotationally.

c) Sequential therapy [25]: It has three steps. 1. Clearing or quick fix phase 2. Transitional phase 3. Maintenance phase

one example is using topical clobetasol propionate and calcipotriol twice a day in phase one, followed by transitional phase in

which the steroid is used on weekends and calcipotriol on weekdays and finally a maintenance phase, in which calcipotriol is continued as long as required with gradual tapering off.

TOPICALLY AVAILABLE TREATMENT FOR PALMOPLANTAR PSORIASIS

1. Salicylic acid (2-10%)
2. Coal tar (1-5%)
3. Anthralin
4. Topical corticosteroids
5. Vitamin D analogues
    a) Calcitriol
    b) Calcipotriol
    c) Tacalcitol
    d) Maxacalcitol
6. Topical psoralen with UVA
7. Topical Retinoid (Tazarotene)
8. Emollients
9. Topical cytostatic therapy
    a) Mechlorethamine (Nitrogen mustard)
    b) Thiotepa

c) 5 - Flurouracil
d) Lomustine
e) Methotrexate gel (1%) [26]

12. Topical allantoin

AVAILABLE SYSTEMIC AGENTS

1. Methotrexate

2. Cyclosporine

3. Retinoids

4. Sulfasalazine

5. Fumaric acid esters

6. Azathioprine

7. Hydroxyurea

8. Mycophenolate mofetil

9. Leflunomide

10.6 Thioguanine

AVAILABLE BIOLOGIC AGENTS

FDA approved a number of biologic agents in january 2003. They include for the treatment of palmoplantar psoriasis. They are

1. Alefacept

2. Efalizumab

3. Etanercept

4. Infliximab

5. Adalimumab

6. Ustekinumab

OTHERS

1. Occlusive agents

2. Photodynamic therapy

3. Monochromatic excimer laser

4. Radiotherapy

5. Pulsed dye laser

Photodynamic therapy, methotrexate, acitretin, cyclosporine are the available therapies for recalcitrant palmoplantar psoriasis.

LET US DISCUSS ABOUT THE TOPICAL THERAPIES ARE USED IN PALMOPLANTAR PSORIASIS

SALICYLIC ACID

Available formulations are Creams, Ointments, Shampoos, Collodion - based paints and gels, Paste (Lassars paste contains salicylic acid and zinc oxide). It deactivates calcipotriol so it should not be combined with it. It should not be combined with UVB also as it blocks its penetration [27].The available strength is 2 – 10%.

COAL TAR

Coal tars are produced by primary condensation of carbonized coal [28]. It has antibacterial, antifungal, anti inflammatory and anti pruritic effect [29]. Since it is messy it is not acceptable to patients. It has been found useful with combination of topical corticosteroid. Crude coal tar LCD (liquor carbonis detergens) is also useful.

Available formulations are cream, lotions, ointment, gel, shampoo,soap and alcohol extract. The contraindications are pre existing

folliculitis, acne, pregnancy and lactation. The available strength is 1 – 5%.

DITHRANOL (0.05%-4%)

It has antiproliferative effect and not suitable for psoriasis over head, neck, flexures and genitalia. The total contact period is 10 minutes / day [30-33]. The available preparations are paste, cream, ointment, stick. It can be combined with topical steroids, PUVA, narrowband UVB, coal tar, calcipotriol, tazarotene, oral cyclosporine and oral retinoids.

VITAMIN A ANALOGUES

Tazarotene (acetylene retinoid) is a third generation retinoid. It is otherwise called as arotenoid and is a prodrug of tazarotenic acid.

Available formulations are cream and gel (0.05 and 0.1% gel). It is applied once daily for three months. The maximum treated area is 10-20%.

VITAMIN D3 ANALOGUES

Since 1990 vitamin D3 is used as a topical agent. Vitamin D receptors present in keratinocytes, Langerhans cells, melanocytes, fibroblasts, endothelial cells, normal breast tissue and breast tumor cells. It inhibits epidermal proliferation, induces keratinocyte proliferation. Due

to fewer side effects and good therapeutic efficacy it is the one of best therapeutic agent for psoriasis [34]. There are four analogues in widespread use; they are calcipotriol, calcitriol, tacalcitol, maxacalcitol.

Mechanism of action

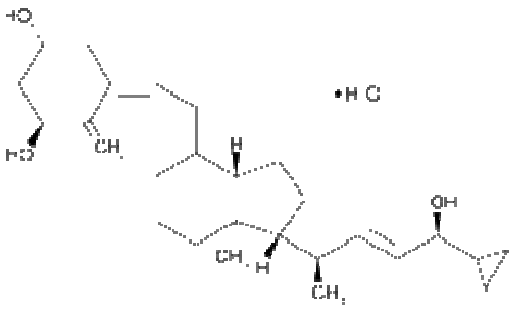
Vitamin D binds with RXR- alpha, which in turn binds with vit D response elements of DNA. It inhibits IL-2, IL-6 production and blocks transcription of IFN- gamma, GM-CSF, also inhibits cytotoxic T cells, NK cells activity. It shifts the Th1 cytokine to Th2. It increases IL– 10 and decreases IL-8.

TOPICAL CALCIPOTRIOL

The effect of the drug is slower than topical corticosteroids (TCS). To attain maximal effect 8-10 weeks of treatment is needed. For rapid activity TCS is combined with topical calcipotriol. It should not be combined with acid products because it is inactivated especially by salicylic acid and hydrocortisone -17-valerate [35]. It is a synthetic vitamin D derivative which acts by binding to vitamin D receptor. Occurrence of hypercalcemia is rare. It induces terminal differentiation and simultaneous inhibition of proliferation of epidermal keratinocytes. Therefore used in disorders characterized by hyperkeratosis, acanthosis, parakeratosis and epidermal hyperproliferation. The maximum quantity

of maintenance dose is 100g /week to prevent hypercalcemia [36]. The concentration is 50 microgram/gm. Treatment is given in three phases namely quick - fix phase, transitionsl phase and maintenance phase. Monitoring of serum or urinary calcium is not required in localized psoriasis. Twice daily clobetasol propionate foam on weekends with twice daily calcipotriol on weekdays led to 92% clearance of psoriatic trunk lesions compared to only 62% with calcipotriol and vehicle after 6 months of treatment [37]. The available formulations are ointment, cream, lotion.

Chemical structure of Calcipotriol



26, 27-cyclo-vitamin D3

22, 23- double bond

Transposition of the 25-OH to the 24 position

It is not applied prior to PUVA because it is inactivated by UVA. Recently a combination of calcipotriol with super potent topical

corticosteroids was used for treatment of psoriasis. The response was rapid and it reduced the irritation [38].

Calcipotriol acts on specific markers of epidermal proliferation (ki 67) and differentiation (keratin 10) and is more selective on T cell subset. This leads to major reduction of CD45RO & CD8 cells.

Corticosteroids increase keratin 10 at the epidermal level without significant effect on ki-67 and reduce NK-T cell receptor.

INDICATIONS

FDA approved for Psoriasis

1. Mild to moderate type (monotherapy or combination)

2. Severe type (combination)

OTHER DERMATOLOGICAL USES

DISORDERS OF KERATINIZATION [42]

1. X linked recessive Icthyosis

2. Lamellar Ichthyosis

3. Epidermolytic hyperkeratosis

4. Sjogren Larsson syndrome

AUTO IMMUNE DISORDERS

1. Morphoea

2. Vitiligo

NEOPLASTIC DERMATOSES

1. Cutaneous T cell lymphoma

2. Cutaneous metastatic breast cancer

MISCELLANEOUS DERMATOSES

1. Acanthosis nigricans

2. Confluent & reticulated papillomatosis

3. Disseminated superficial actinic porokeratosis

4. Erythema annulare centrifugum

5. Grover's disease

6. Inflammatory linear verrucous epidermal nevus

7. Keratosis lichenoides chronica

8. Pityriasis rubra pilaris

9. Prurigo nodularis

10. Seborrhoeic dermatitis

CONTRAINDICATIONS

There are no absolute contraindications for calcipotriol. The relative contraindications are conditions causing hypercalcemia, abnormality in bone or calcium metabolism, renal insufficiency, allergy to vitamin D3 analogues, pregnancy & lactation.

PREGNANCY – category C

SIDE EFFECTS

The side effects are local irritation in 20% of patients, itching and redness

TOPICAL CORTICOSTEROIDS

Since 1950, topical corticosteroid is the most useful therapy. In 1950 Nobel Prize was given to Henoch, Kendall and Reichstein for the development of cortisone. Steroids have been used for 6-8 wks for palmo plantar psoriasis.

Pharmacokinetics action depends on the structure of molecule, vehicle and application site. TCS preparations are evaluated with the vasoconstriction assay.

CLASSIFICATION OF TOPICAL CORTICOSTEROIDS [43]

CLASS I super potent:

Clobetasol propionate gel, ointment,cream and lotion 0.05%

Betamethasone dipropionate gel* and ointment* 0.05%

Diflorasone diacetate ointment* 0.05%

Fluocinonide cream 0.1%

Flurandrenolide tape 4µg/cm2

Halobetasol propionate ointment and cream 0.05%

CLASS II High potent:

Amcinonide ointment 0.1%

Betamethasone dipropionate cream* and ointment 0.05%

Clobetasol propionate solution (scalp application) 0.05%

Desoximethasone ointment , cream 0.25% and gel 0.05%

Diflorasone diacetate ointment and cream* 0.05%

Fluocinonide gel, ointment, cream and solution 0.05%

Halocinonide ointment and cream 0.1%

Mometasone furoate ointment 0.1%

CLASS III High Potent:

Amcinonide cream and lotion 0.1%

Betamethasone dipropionate cream and lotion 0.05%

Betamethasone valerate ointment 0.1%

Desoximethasone cream 0.05%

Diflorasone diacetate cream 0.05%

Fluticasone propionate ointment 0.005%

Triamcinolone acetonide ointment 0.1% and cream 0.5%

CLASS IV Medium potent:

Betamethasone valerate foam 0.12%

Fluocinolone acetonide ointment 0.025%

Flurandrenolide ointment 0.05%

Hydrocortisone valerate ointment 0.2%

Momentasone furoate cream and lotion 0.1%

Triamcinolone acetonide ointment and cream 0.1%

CLASS V Medium potent:

Betamethasone dipropionate lotion 0.05%

Betamethasone valerate cream and lotion 0.1%

Clocortilone pivalate cream 0.1%

Fluocinolone acetonide cream 0.025% and oil 0.01%

Fluocinolone propionate cream and lotion 0.05%

Flurandrenolide cream and lotion 0.05%

Hydrocortisone valerate cream 0.2%

Hydrocortisone probutate cream 0.1%

Prednicarbate ointment and cream 0.1%

Triamcinolone acetonide lotion 0.1%

CLASS VI Low potent:

Aclomethasone dipropionate ointment and cream 0.05%

Triamcinolone acetonide cream 0.1%

Betamethasone valerate lotion 0.1%

Desonide gel,ointment, cream, lotion and foam 0.05%

Fluocinolone acetonide cream 0.01% and solution 0.05%

Triamcinolone acetonide cream and lotion 0.025%

CLASS VII Low potency:

Topicals with hydrocortisone, dexamethasone and prednisolone

*Optimized vehicle

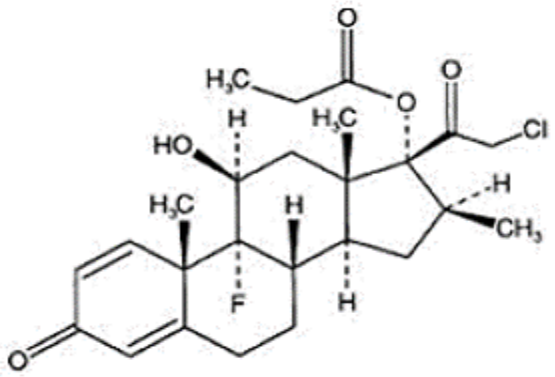
STRUCTURE OF TOPICAL CORTICOSTEROID

Hydrocortisone is the backbone of the topical corticosteroid molecule. Hydrocortisone is the parent compound of modern glucocorticosteroid derivatives. In 1952, Sulzberger used topical hydrocortisone for eczematous eruption for the first time. It has cyclopentanoperhydrophenanthrene nucleus with high glucorticosteroid and low mineralocorticoid activity [44].

Enzymes in the epidermis cause deesterification of topical corticosteroid into active metabolite. Halogenation at the 21 portion inhibits de esterification at the 17 portion and increase the potency. Halogenation of the 9 th position leads to high glucocorticoid activity.

STRUCTURE OF CLOBETASOL PROPIONATE

Vasoconstriction potency rating is class I superpotent 0.05%



Functional groups

C1, 2: double bond

C9: fluorine

C16: methyl

C17: ester

C21: chlorine

TOPICAL CORTICOSTEROIDS MECHANISM OF ACTION

Corticosteroids are therapeutic by virtue of their anti-inflammatory, antiproliferative, immuosuppressive and vasoconstrictive properties. The action is mediated by its binding to the glucocorticoid receptor in the cytoplasm of the cell. This complex binds to acceptor sites on DNA and after that gene regulation and transcription of mRNA occur [45-47].

Anti-inflammatory effects

Vascular sensitivity is reduced by preventing the release of prostaglandins, platelet activating factor and inhibition of mast cell sensitization which cause histamine release. Vascular permeability is decreased by induction of anti inflammatory proteins like lipocortin, vasocortin, vasoregulin and hence decrease the release of arachidonic acid, prostaglandins. It decreases the production of inflammatory mediators IL-1α, IL-1β, INF- gamma, TNF, IL-2 and GM-CSF.

Antiproliferative and atrophogenic effects

Corticosteroids reduce the thickness of epidermal layer, reduce mitoses and growth factors. In the dermis it causes atrophy by reduced dermal volume, hypoactive fibroblasts and fragility of dermal vessels.

INDICATIONS

Dermatitis and papulosquamous disorders

1. Atopic dermatitis
2. Diaper dermatitis
3. Dyshidrotic eczema
4. Erythroderma

5. Lichen planus
6. Lichen simplex chronicus
7. Nummular dermatitis
8. Pityriasis rosea
9. Palmoplantar, plaque and intertriginous type of psoriasis,
10. Seborrhoeic dermatitis

Bullous dermatoses

1. Bullous pemphigoid
2. Cicatricial pemphigoid
3. Epidermolysis bullosa acquisita
4. Pemphigus foliaceous
5. Pemphigoid gestationis

Connective tissue disease

1. Lupus erythematosus
2. Dermatomyositis

Neutrophilic dermatoses

1. Pyoderma gangrenosum
2. Behcets disease

OTHERS

1. Alopecia areata
2. Acne keloidalis nuchae
3. Cutaneous T cell lymphoma
4. Granuloma annulare
5. Jessners lymphocytic infiltrare
6. Lichen plano pilaris
7. Lichen sclerosus et atropicus
8. Morphoea
9. Vitiligo
10. Wells syndrome

CONTRAINDICATIONS

ABSOLUTE

Known hypersensitivity to topical corticosteroids

RELATIVE

Bacterial, viral, fungal, mycobacterial infections , infestations and ulcerations

ADVERSE EFFECTS

A) Local side effects are hypopigmentation, wrinkled skin, pseudo scar, striae , purpura, steroid addiction, glaucoma, allergic contact dermatitis, irritant contact dermatitis, tachyphylaxis, folliculitis, miliaria, perioral dermatitis, rosacea, acneiform eruptions, crusted scabies, telangiectasia, erythema, purpura.

B) Systemic side effects are suppression of hypothalamic pituitary adrenal axis, iatrogenic cushing syndrome, growth retardation in infants and children

AVAILABLE PREPARATIONS

Ointment, cream, gel, lotion, solution,foams,sprays and tapes [48]. Ointment form has the highest efficacy. The optimal improvement within 2 weeks and 74% of patients remained in remission.

Topical Corticosteroids are frequently used in combinations with topical vitamin D analogues, calcineurin inhibitors, coal tar, anthralin, tazarotene, systemic drugs and photo therapy. Combination of corticosteroids with topical vitamin D analogue is more potent.

DOSE

The recommended dose for adult is less than 45gm/week and for infants & children is less than15gm/week.

In this combination regimen of calcipotriol and steroid, calcipotriol is well tolerated and the irritation of vitamin D derivative is reduced [39]. The immunosuppressive effect of calcipotriol on T helper cells are augmented by corticosteroids [40].The combination of clobetasol and calcipotriol ointment is significantly more effective than monotherapy for short-term treatment. Weekday calcipotriol plus weekend pulse clobetasol ointment shows a consistent trend toward greater maintenance of remission [37, 41]. It is safe for upto 52 weeks. Exacerbation of psoriasis occurred in 10-15% of patients and disappeared after discontinuation of treatment. Tacalcital ointment is the least irritating agent.

PHOTOCHEMOTHERAPY

History

Phototherapy is the use of ultraviolet light for skin disorders. The treatment for skin diosorders used from 1400 BC in India [49]. Psoralen is found in plants (lemon, lime, fig gloves, bergamot, babache) [50]. 8 methoxy psoralen & 5 methoxy psoralen are natural psoralens. 8 MOP is derived from the plant Ammi Majus. 5 MOP is derived from

psoralea corylifolia. 4, 5, 8 Trimethyl psoralen, 3 Carbethoxy psoralen are synthetic psoralens.

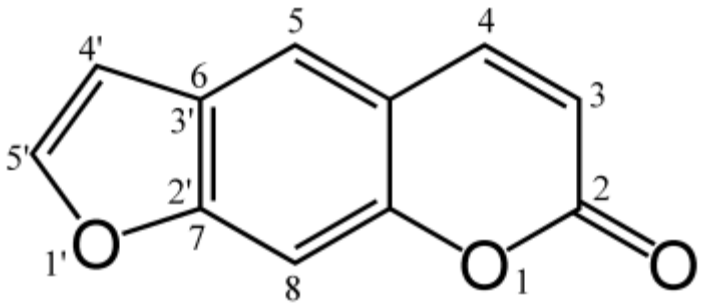
In 1903 Nobel Prize was awarded to Niels Finsen for the treatment of lupus vulgaris by UV irradiation [51]. In USA FDA gave approval for PUVA therapy in 1982. In 1976 Fisher, reported on the action spectrum for psoriasis. Combined use of psoralen with long wave UV irradiation is called as psoralen photo chemotherapy. In 1972 Mortazawi developed oral PUVA therapy for psoriasis. It was popularized in 1974 by Parrish and Fitzpatrick et al [52]. PUVA with topical psoralen was introduced in 1975 by Mortazawi and Obertse-Lehn. Bath PUVA was developed in 1977 by Born.

Psoralens are tricyclic furocoumarins derived from plants. 8-MOP and 5-MOP are currently available oral preparations which contain either crystals, micronized crystals or solubilized psoralens. Oral dosage 8 methoxy psoralen 0.6mg/kg given one and half hours before irradiation. Its absorbtion is decreased by fatty meal. It will be active upto 8 -12 hours.

High intensity fluorescent UVA tubes are used. UVA dose is increased 0.5-1.5J/cm2 per sitting. If psoriasis clears after therapy PUVA will be stopped.

UVA spectrum ranges from 320-400nm.UVA radiation penetrate the epidermis, papillary dermis & superficial vascular plexus. After radiation topical sunscreen should be given to all patients.

PSORALEN CHEMICAL STRUCTURE



Principle

UV radiation is produced artificially by following mechanisms. Electric current is passed through a gas (mercury) ---> mercury atoms excited by passing electrons through the lamp's electrode ---> It releases energy and they are absorbed as optical radiation (UV rays)

LAMPS [53]

1. Fluorescent lamp

2. Metal halide lamp (high pressure)

3. Discharge lamp

4. Conventional incandescent lamp

5. Halogen incandescent lamp

6.Mercury vapour lamp (low pressure & high pressure mercury lamp, low pressure & high pressure sodium lamp, high pressure xenon lamp, high pressure krypton lamp, metal vapour lamp)

7. Xenon short arc lamp

ULTRAVIOLET LIGHT

The wavelength of the ultraviolet light ranges from 200-400nm.

UVC (germicidal reaction - 200-290 nm): It does not reach the earth's surface because it is absorbed by ozone layer. It can penetrate upto reticular dermis.

UVB (sunburn spectrum – 290-320): Most of the sunscreens are used against this spectrum. It can penetrate upto papillary dermis.

UVA (black light): It can penetrate the epidermal layer.

UVA1: 340-400 nm.

UVA2: 320-340nm.It is more effective and more damaging to normal skin.

Precautions & Advice

Protect the eyes with goggles, face with a pillow case and male genitals with an athletic support. Sunlight exposure should be avoided eight hours after radiation. Sunscreen should be given after radiation.

UV RADIATION DOSIMETRY

The exposure dose (J/cm2) is calculated from irradiance and exposure time. Exposure dose = Irradiance × exposure time.

The basic unit of power is watt. Watt=Joules/second

Joule is the basic unit of energy.

Irradiance is the power delivered per unit area of surface (W/cm2).

MINIMAL PHOTOTOXIC DOSE

Lowest dose of UVA that causes erythema (grade1) 72 hours after exposure to UVA. Minimal phototoxic dose is measured by using an automated skin testing UVA irradiation unit. It is very difficult to calculate on Indian skin.

GRADING OF ERYTHEMA

Grade 0 – No erythema

1 – Minimal erythema (pink colour)

2 – Marked erythema (red colour)

3 – Erythema and edema (fiery red)

4 - Erythema, edema and blister (fiery red)

MECHANISM OF ACTION [54, 55]

It has three steps.

1. Psoralen binds with DNA double strand before irradiation [56-58].

2. After UVA exposure bind with pyrimidine base to form cyclobutane monoadducts(MA).

3. After absorbing a second photon, psoralen-DNA crosslink is formed by 4MA.The reactive oxygen species are formed by this cross link, it damages cell membrane. This cross link inhibits DNA replication causing cell cycle arrest. So there is alteration of cytokine & cytokine receptor which causes apoptosis of lymphocytes & keratinocytes.

PHASES OF PUVA THERAPY

Clearing phase : The clearing phase starts with the commencement of therapy and ends with clearance of at least 95% of lesions.

Maintenance phase : It stars after 95% clearance of lesion. The final clearance dose of irradiation is constant and the frequency of treatment is gradually tapered.

Tapering dose :

Weekly once

Then,

Two weeks once

Then,

Three weeks once

Then,

Four weeks once

Then,

Stop treatment [77, 78]

TYPES OF PSORALEN

1) Natural – 8 Methoxy psoralen (8 MOP)

5 Methoxy psoralen (5 MOP)

2) Synthetic - 4, 5, 8, Trimethyl psoralen

carbethoxy psoralen (3 CP) [59,60]

INDICATIONS FOR PHOTOCHEMOTHERAPY [62-65]

1. Psoriasis

2. Vitiligo

3. Atopic dermatitis

4. Seborrhoeic dermatitis

5. Alopecia areata

6. Pityriasis rubra pilaris

7. Lichen nitidus

8. Urticaria pigmentosa

9. Actinic prurigo

10 .Pityriasis lichenoides

11. Mycosis fungoides

12. Langerhans cell histiocytosis

13. Lymphomatoid papulosis

CONTRAINDICATIONS [66]

1. Previos exposure to inorganic arsenic & radiotherapy

2. H/O cutaneous malignancy

3. Genodermatoses like xeroderma pigmentosum and Blooms syndrome

4. Lupus erythematosus

5. Pemphigus vulgaris and bullous pemphigoid

6. Pregnancy and lactation

7. Children ≤ 18 years

8. Previous cumulative therapy (>2000J/cm2)

9. Pustular and erythrodermic psoriasis

10. Liver and kidney failure

11. Cardiac dysfunction

12. Cataract

CARCINOGENIC EFFECTS

UVA radiation can aggravate the skin tumors in patients with xeroderma pigmentosum and basal cell nevus syndrome.

SYSTEMIC PSORALENS

The available systemic psoralens are

8 Methoxy psoralen

5 Methoxy psoralen – it has less gastrointestinal side effect.

Trimethyl psoralen

3-carbethoxy psoralen

ORAL PUVA

8-MOP– It is given one and half hours before UVA 2-3 times/week. The dose is calculated according to patient body weight 0.8mg/kg. Single capsule contains 10mg.

5-MOP (1.2mg/kg) – It is given 2 hrs before UVA.

ADVERSE EFFECTS [63]

SHORT TERM EFFECTS

a) Adverse effects due to psoralen

Nausea, vomiting, headache, dizziness, bronchoconstriction, drug fever and hepatotoxicity.

b) Phototoxic effect

Erythema, pruritus , pain, photo onycholysis, phytophoto dermatitis , blistering on hands and feet.

c) Others

Hypertrichosis, acneiform eruptions, bullous pemphigoid and subungual haemorrhage of finger nails.

LONG TERM EFFECT [59]

Chronic actinic damage,melanoma , squamous cell carcinoma and cataract.

TOPICAL PUVA THERAPY

1) BATH PUVA

Trimethyl psoralen with UVA phototherapy was pioneered in Finland & Sweden**.** Synthetic furocoumarin 4, 5, 8-trimethyl psoralen is

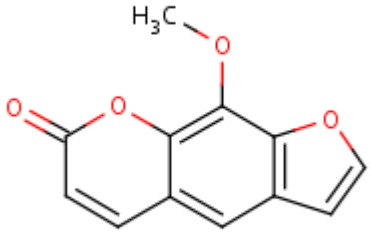
used for bath PUVA. 50 mg dissolved in 100 ml of ethanol and mixed in 150 L of water at body temperature [67].

2)SOAK PUVA

To avoid the side effects of systemic PUVA topical PUVA is useful. It has shown good results. Hand and/or foot soak in 8MOP 2.5 mg/l for 15 minutes followed by UVA irradiation weekly two or three times is effective. 1 ml contains 5 mg of 8 MOP [67]. In the literature there is no specific data regarding the initial dose of UVA irradiation for palmoplantar psoriasis. It depends upon the severity of the disease and higher UVA doses are recommended to treat the thicker skin of palmoplantar psoriasis [68].

It is not associated with gastro intestinal tract and carcinogenic effects. Moisturization is needed before phototherapy in elderly populations because phototherapy itself can aggravate xerosis and pruritus [69]. The emollients will decrease the total UVA dose required to clear psoriasis [61.70]. Alternatively 5mg Trimethylpsoralen (TMP) in 10 ml of ethanol can be used and mixed in 15 litres of water.

8-METHOXY PSORALEN CHEMICAL STRUCTURE



OTHER FORMULATIONS

Cream and gel formulations (0.005% solution of aqueous 8-MOP gel) applied over the affected site for 15 minutes followed by UVA exposure 2 hours later. TMP bath UVA can be combined with oral etretinate or acitretin. The risk of skin cancer is less with topical PUVA than systemic PUVA. The dose of UVA is 15-20 times lower with bath PUVA. Bath PUVA with 8 MOP (2.6-3.7mg/l) is also successful. Bath temperature is 37°c and bath time is 15 minutes.

OTHER TOPICAL COMBINATIONS WITH PUVA

Emollients will decrease the minimal phototoxic dose. Keratolytics should be given after phototherapy. Because it increases the minimal phototoxic dose. Patient dislikes like anthralin with PUVA, because it stains the clothes. Vitamin D analogues and tazarotene

decrease the duration of therapy and number of visits. For rapid clearance corticosteroids are useful.

CONTRAINDICATED COMBINATIONS

Acitretin with cyclosporine should not be given. Acitretin inhibits cytochrome p450. So cyclosporine level will be increased [71, 74]. Cyclosporine with PUVA combinations will increase the risk for squamous cell carcinoma either simultaneously or sequentially [72, 73]. Tar with PUVA both will cause Phototoxicity. Methotrexate with cyclosporine both are immunosuppressants.

MATERIALS AND METHODS

STUDY DESIGN

Prospective randomized control study.

TOTAL POPULATION

50

STUDY PERIOD

The treatment duration was six months and the follow up period was six months.

COLLECTION OF DATA AND SOURCES

1. The study was conducted in Coimbatore medical college Hospital from December 2011 to November 2012.
2. The population for the study included patients attending outpatient Department of Dermatology, Coimbatore Medical College Hospital, Coimbatore.
3. The results were tabulated and appropriate tests of significance were worked up.

INCLUSION CRITERIA

1. Patients aged between 18-60 years.
2. Patients who have not used other forms of topical treatment during the previous four weeks.
3. Patients who have given written consent.

EXCLUSION CRITERIA

1. Age less than 18 years.
2. Pregnant and lactating women.
3. Patients who have not given consent.
4. Concurrent immunosuppressive therapy and premalignant skin disease.
5. Significant hepatic and renal dysfunction.
6. Hypertensive and diabetic patients.

PATIENT EVALUATION

History

General examination

Systemic examination

Dermatological examination

Laboratory investigations

a) Complete blood count
b) Urine routine
c) Biopsy

TREATMENT PROTOCOL

Patients under inclusion criteria were arranged randomly into two groups A and B.

GROUP A

25 patients were included in this group. 0.5 ml of 1% 8 Methoxypsoralen lotion was diluted in two litres of water. Hands and feet were soaked in that solution for 15 minutes. Then patient was advised to mop both palms and soles and to apply emollients followed by UVA exposure, 30 minutes after soak. Initial dose of UVA is 1 J/cm^2 with

increment dose of 0.5 J/cm^2 on every visit with a frequency of two times per week for six months. Eyes were protected by using goggles during treatment.

GROUP B

25 patients were included in this group. Sequential therapy of 0.05% Clobetasol propionate ointment with 0.005% Calcipotriol ointment was given for six months.

PHASE 1: combination of clobetasol propionate and calcipotriol ointment once a day application in the first month.

PHASE 2: clobetasol propionate for weekends and calcipotriol for week days once a day application in the second and third month.

PHASE 3: calcipotriol ointment once a day application in the fourth, fifth and sixth month.

TREATMENT ASSESMENT

Severity and extent of disease were calculated by using "Psoriasis Area Severity Index score" (PASI Score) and PASI percentage reduction score**.** PASI score was calculated before treatment, at the end of 8^{th} week, 16^{th} week and 24^{th} week.

PASI score for Palmoplantar psoriasis

$$PASI = 0.2\ (EU + IU + DU)\ AU + 0.4\ (EL + IL + DL)\ AL$$

Area of Psoriatic involvement for Palms and Soles were calculated as 1. It means 10% of area was involved. Severity of Erythema, Induration, Desqumation was calculated as follows 0 – None, 1 – Slight, 2 – Moderate, 3 – Severe, 4 – Very Severe.

OBSERVATIONS

AGE DISTRIBUTION

In Group A the range of mean age in this study was 43.32 ± 15.70 years SD. In Group B the range of mean age in this study was 39.12±14.12 SD.

Age (In years)	Group A	Group B
19-20	3	3
21-30	4	6
31-40	5	5
41-50	4	4
51-60	5	6
61-70	4	1
Total	**25**	**25**

Table No .1 AGE DISTRIBUTIONS IN THE RANGE

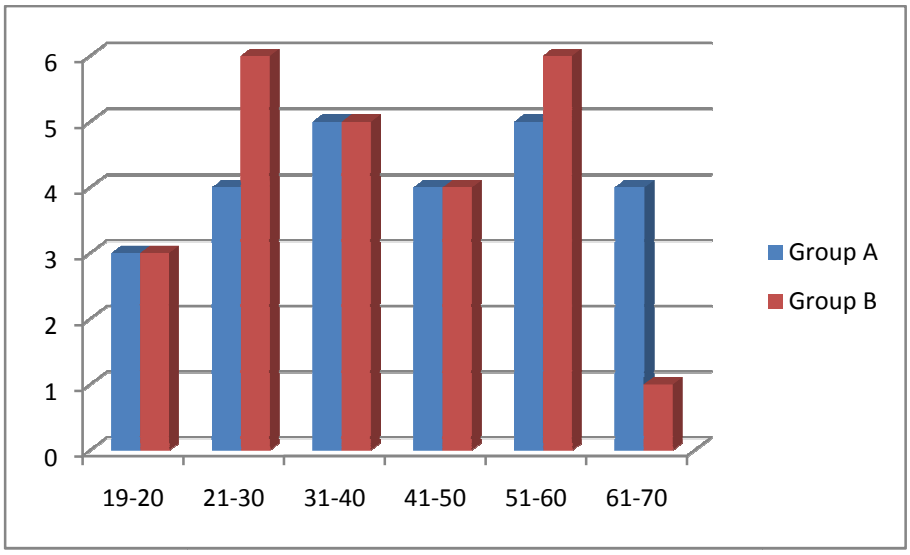


Chart No .1 AGE DISTRIBUTIONS IN THE RANGE

GROUP	MEAN AGE (YEARS)
A	43.32
B	39.12

Table No.2 MEAN AGE DISTRIBUTION

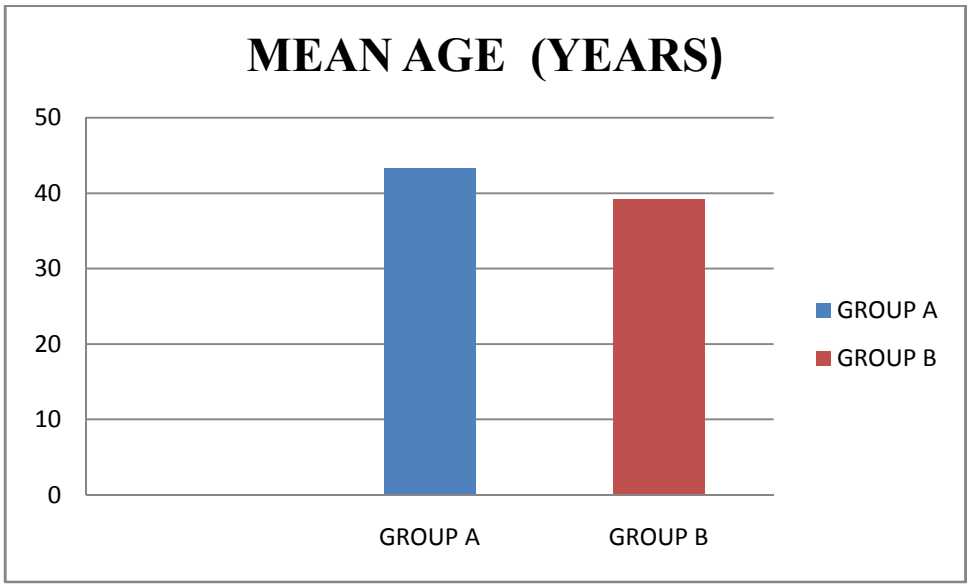


Chart No.2 MEAN AGE DISTRIBUTION

SEX DISTRIBUTION

In group A76 % patients were males, 24 % patients were females. In Group B 60 % patients were males, 40 % patients were females.

The overall male to female ratio was 34:16 (68%: 32%).

GROUP	MALES	FEMALES
A	76%	24%
B	60%	40%

Table No.3 SEX DISTRIBUTION

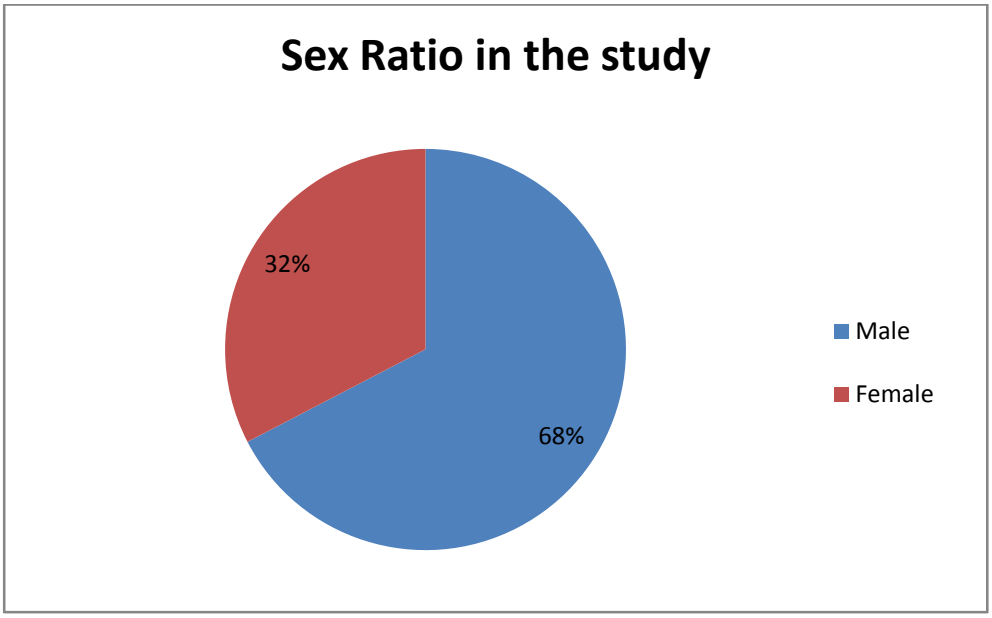


Chart No.3

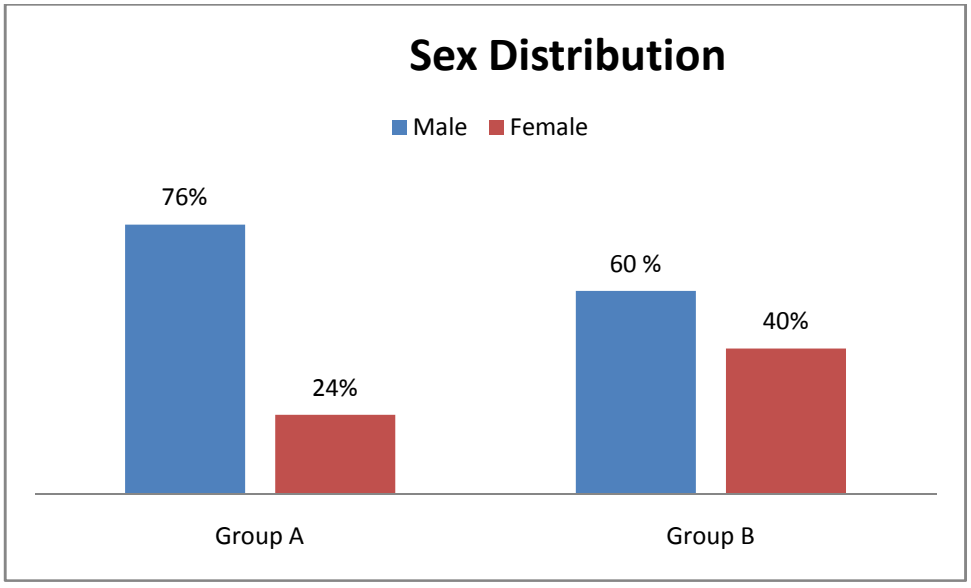


Chart No.4

DURATION OF DISEASE

In Group A the range of mean duration of the disease in this study was 17.24±12.20 months SD. In Group B the range of mean duration was 17.08±14.67 months SD.

GROUP	MEAN DURATION (MONTHS)
A	17.24
B	17.08

Table No. 4 MEAN DURATION OF DISEASE

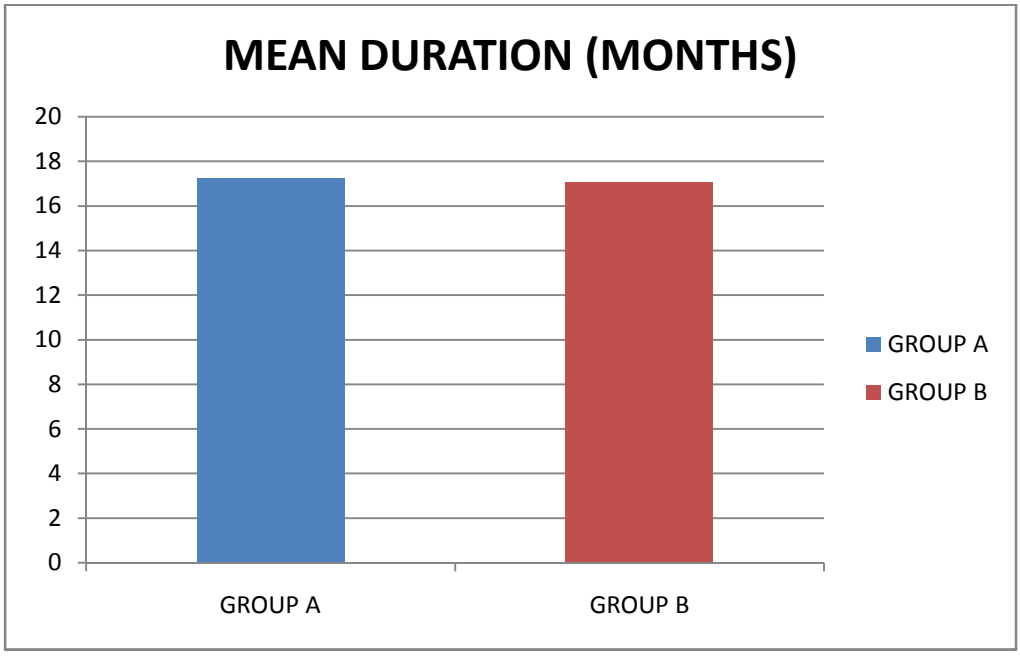


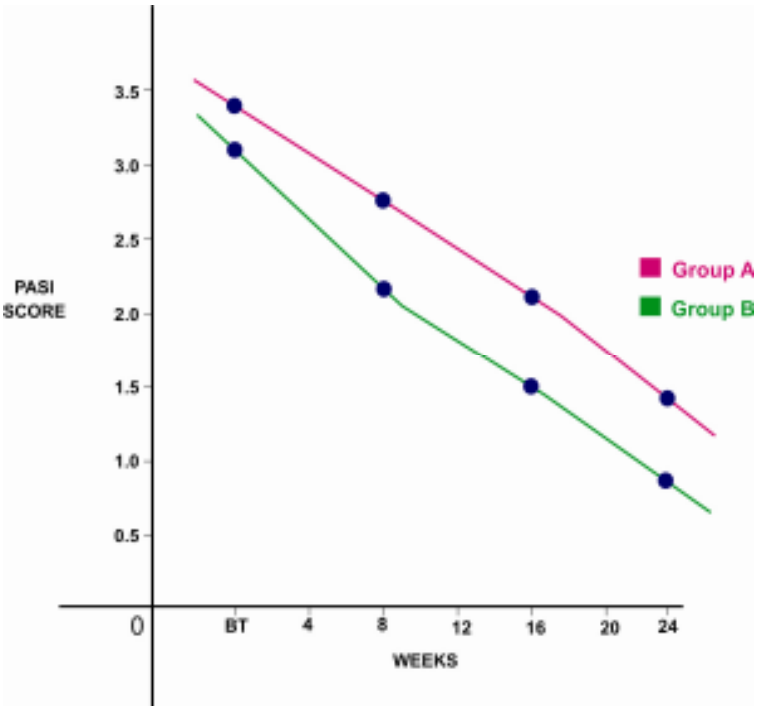
Chart No.5

PASI REDUCTION SCORE

According to graph the mean PASI score before treatment for Group A and Group B were 3.4 and 3.1 respectively. After eight weeks of treatment the mean PASI score for both Groups were 2.7 and 2.2 respectively. After sixteen weeks of treatment the mean PASI score for both groups were 2.1 and 1.5 respectively. After twenty four weeks of treatment the mean PASI score for both groups were 1.4 and 0.9 respectively.

GROUP	PASI SCORE			
	BEFORE TREATMENT	8 WKS	16 WKS	24 WKS
A	3.4	2.7	2.1	1.4
B	3.1	2.2	1.5	0.9

Table No.5 PASI REDUCTION SCORE



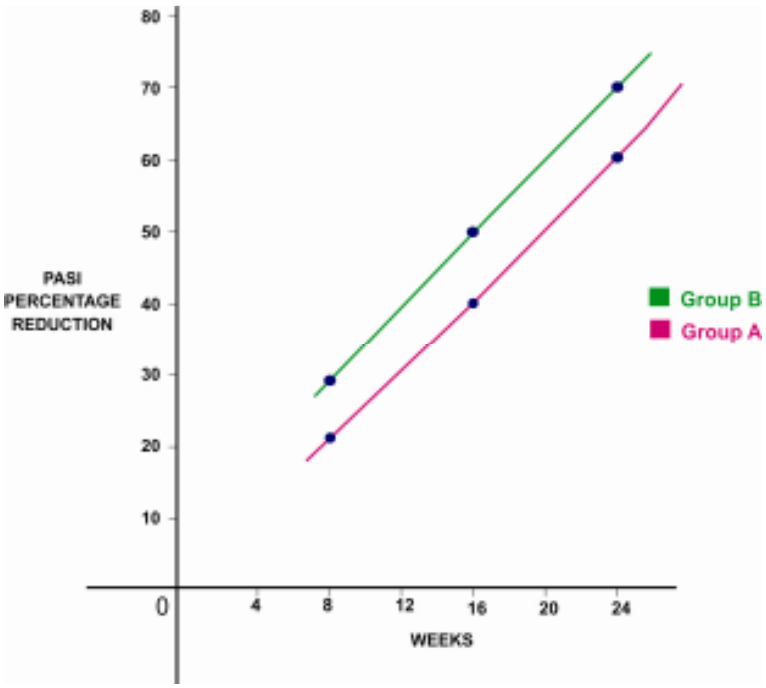
Graph No.1

PASI PERCENTAGE REDUCTION

From the graph after eight weeks of treatment the mean PASI percentage reduction for both groups were 21.28% and 29.55% respectively. After sixteen weeks of treatment the mean PASI percentage reduction for both groups were 40.66% and 50.56% respectively. After twenty four weeks of treatment the mean PASI percentage reduction for both groups were 60.50% and 70.77% respectively.

GROUP	PASI PERCENTAGE REDUCTION		
	8 WEEKS	16 WEEKS	24 WEEKS
A	21.28%	40.66%	60.50%
B	29.55%	50.56%	70.77%

Table No.6 PASI PERCENTAGE REDUCTION DURINGTREATMENT



Graph No.2

SL.NO	PASI PERCENTAGE(%) REDUCTION AT THE END OF TREATMENT	GROUP A	GROUP B
1	10-20	-	-
2	21-30	-	-
3	31-40	-	-
4	41-50	4	2
5	51-60	8	2
6	61-70	7	4
7	71-80	3	11
8	81-90	-	5
	TOTAL	**22**	**24**

Table No.7 PASI PERCENTAGE REDUCTION AT THE END OF TREATMENT IN PALMOPLANTAR PSORIASIS

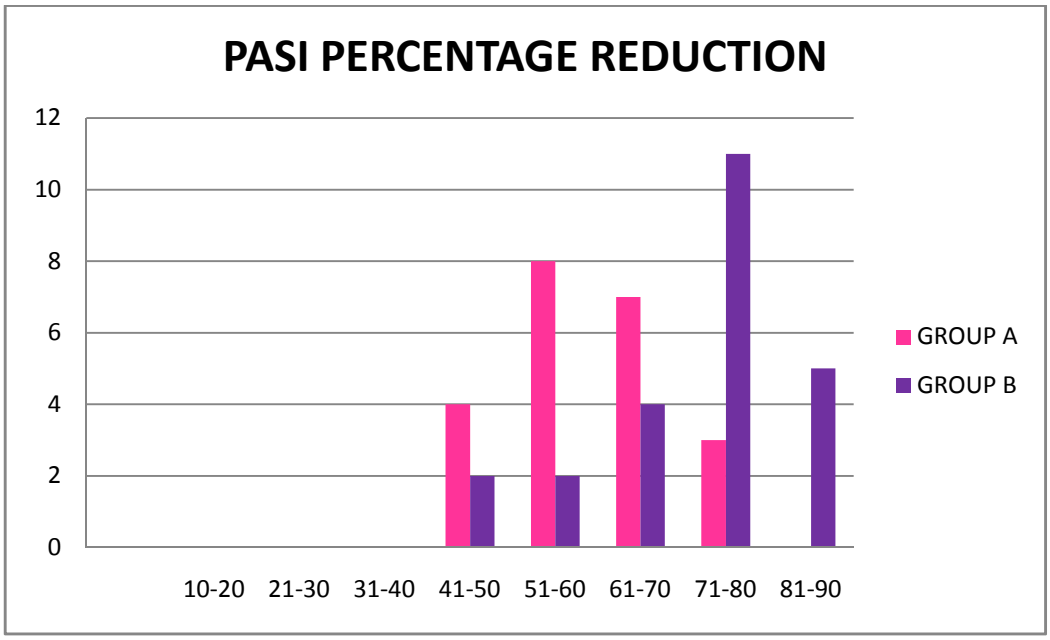


Chart No.6

ADVERSE EFFECTS

GROUP A

Four patients (18.18%) developed adverse effects during treatment. Two patients developed erythema over palms and soles, two patients developed burning sensation.

GROUP B

Three patients (12.5%) developed adverse effects during treatment. One patient developed erythema over soles and two patients developed itching and burning sensation over soles.

GROUP	ADVERSE EFFECT
A	4 Patients (18.18%)
B	3 Patients (12.5%)

Table No.8 ADVERSE EFFECTS

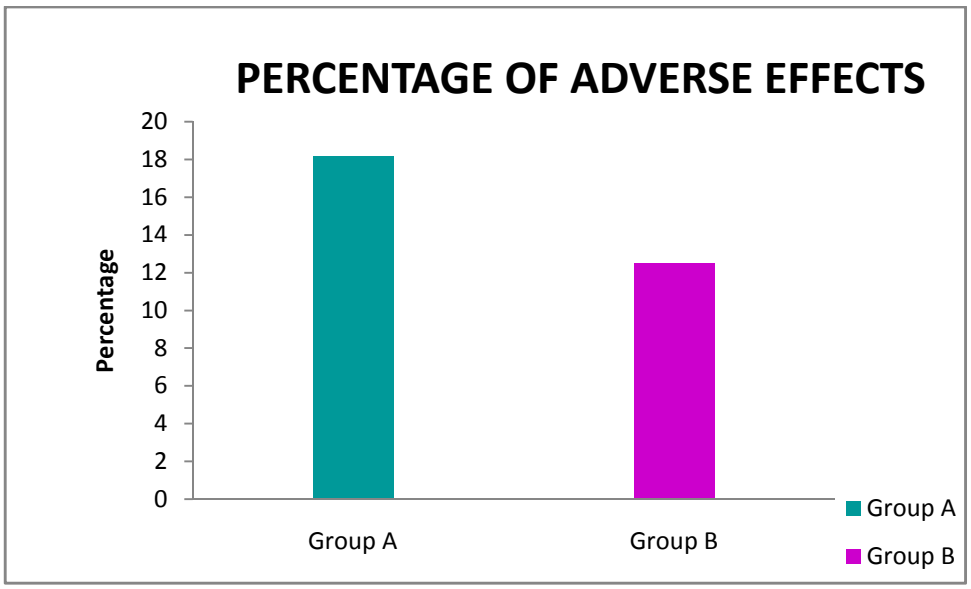


Chart No.7

STATISTICAL DATA ANALYSIS

Out of 25 patients selected for group A and group B, 22 patients came for treatment till twenty four weeks in group A, 24 patients came for treatment till twenty four weeks in group B. Only those patients were included for analysis.

76% of patients in group A were males, remaining 24% patients were females. In group B 60% patients were males, remaining 40% patients were females. Average age of group A patients were 43.32±15.70 years SD. Average age of group B patients were 39.12±14.12years SD. Average duration of disease in group A patients were 17.24±12.20 months SD. Average duration of disease in group B patients were 17.08±14.67 months SD. However Chisquare test did not show any significant association (X^2 =0.827 P>0.05) between groups and genders.

The average initial PASI score before treatment for group A was 3.35±1.13 SD, for group B was 3.08±1.36 SD. The t test results did not show any significant difference in the average initial score between group A and group B. (t value =0.753 P>0.05)

Analysis of group A

The initial score was compared with eighth week score for group A. It was found that the initial score was 3.3545 before treatment and it reduced to 2.67 with an average reduction in the score being 0.6818 and percentage reduction was 21.28%. The t test result showed significant difference at eighth week. (t value = 10.035 $P<0.01$)

At the end of sixteenth week it reduced to 2.0545 with an average reduction in the score being 1.300 and percentage reduction was 40.06%. The t test result showed significant difference at sixteenth week. (t value =12.889 $P<0.01$)

At the end of twenty fourth week it reduced to 1.3727 with an average reduction in the score being 1.9818 and percentage reduction was 60.50%. The t test showed significant difference at twenty fourth week. (t value = 13.754 $P<0.01$)

Paired sample t test conducted for group A comparing initial scores with scores at eighth, sixteenth, twenty fourth week showed significant reduction in the scores at all three periods.

Analysis of group B

The initial score was compared with eighth week score for group B. It was found that the initial score was 3.0750 before treatment and it reduced to 2.1583 with an average reduction in the score being 0.9167 and percentage reduction was 29.55%. The t test showed significant difference at eighth week. ($t = 8.571$ $P<0.01$)

At the end of sixteenth week it reduced to 1.5083 with an average reduction in the score being 1.5667 and percentage reduction was 50.56%. The t test showed significant difference at sixteenth week. ($t = 9.603$ $P<0.01$)

At the end of twenty fourth week it reduced to 0.8583 with an average reduction in the score being 2.2167 and percentage reduction was 70.77%. The t test showed significant difference at twenty fourth week. ($t=9.843$ $P<0.01$)

Paired sample t test conducted for group B comparing initial scores with scores at eighth, sixteenth, twenty fourth week showed significant reduction in the scores at all three periods.

Analysis of both group A and group B

Comparison of percentage reduction for group A and group B at eighth week showed the group A patients had an average reduction of 21.28%±9.30 SD. Whereas group B patients had an average reduction of 29.55%±11.83SD. The t test showed significant difference in the percentage reduction in the scores between group A and group B at eighth week. ($p<0.01$)

At sixteenth week group A patients had an average reduction of 40.06±10.90 SD. Whereas group B patients had an average reduction of 50.56±10.74 SD. The t test showed significant difference in the percentage reduction in the scores between group A and group B. ($p<0.05$)

At twenty fourth week group A patients had an average reduction of 60.50±10.26 SD. Whereas group B patients had an average reduction of 70.77±10.66 SD. Here the t test showed significant difference in the percentage reduction in the scores between group A and group B. ($p<0.05$)

		Mean	S.D	t Value	P Value
Pair 1 (After 8 Weeks)	A	21.28	9.30	2.618	P<0.01
	B	29.55	11.83		
Pair 2 (After 16 Weeks)	A	40.06	10.90	3.288	P<0.05
	B	50.56	10.74		
Pair 3 After (24 Weeks)	A	60.50	10.26	3.324	P<0.05
	B	70.77	10.66		

Table No.9 PAIRED SAMPLE STATISTICS TABLE FOR PASI PERCENTAGE REDUCTION

RESULTS

GROUP A

Out of 22 patients, 20 (90%) showed more than 50% reduction of PASI score. None of the patient showed complete clearance of both palmar and plantar psoriasis. Four patients showed complete clearance of lesion in the palms. Two patients showed complete clearance of lesion in the soles. The average period of clearance of lesions was at 19 weeks. In six months follow up period 3 patients showed relapse after 15 weeks of average period of remission.

GROUP B

Out of 24 patients, all patients (100%) showed more than 50% reduction of PASI score. Here also none of the patient showed complete clearance of both palmar and plantar psoriasis. Seven patients showed complete clearance of lesion in the palms and five patients showed complete clearance of lesion in the soles. The average period of clearance of lesions was at 20.3 weeks. In six months follow up period 2 patients showed relapse after 20 weeks of average period of remission.

S.No	Remission (weeks)				Relapse (weeks)			
	Group A		Group B		Group A		Group B	
	P	PL	P	PL	P	PL	P	PL
1	17	-	22	-	-	-	-	-
2	16	-	23	-	-	-	-	-
3	20	-	19	-	-	-	-	-
4	18	-	17	-	13	-	-	-
5	-	22	16	-	-	20	-	-
6	-	21	20	-	-	12	-	-
7	-	-	15	-	-	-	-	-
8	-	-	-	24	-	-	-	-
9	-	-	-	22	-	-	-	20
10	-	-	-	21	-	-	-	-
11	-	-	-	20	-	-	-	-
12	-	-	-	24	-	-	-	20

Table No.10 REMISSION AND RELAPSE

.

Image No.1 HAND FOOT PUVA CHAMBER

Image No.2 PUVA THERAPY

BEFORE TREATMENT

20 WEEKS AFTER TREATMENT

Image No. 3 PUVA THERAPY

BEFORE TREATMENT

21 WEEKS AFTER TREATMENT

Image No.4 PUVA THERAPY

BEFORE TREATMENT

17 WEEKS AFTER TREATMENT

Image No.5 CALCIPOTRIOL COMBINATIONS

BEFORE TREATMENT

17 WEEKS AFTER TREATMENT

Image No. 6 CALCIPOTRIOL COMBINATIONS

BEFORE TREATMENT

20 WEEKS AFTER TREATMENT

Image No. 7 CALCIPOTRIOL COMBINATIONS

BEFORE TREATMENT

19 WEEKS AFTER TREATMENT

Image No. 8 CALCIPOTRIOL COMBINATIONS

BEFORE TREATMENT

21 WEEKS AFTER TREATMENT

Image No. 9 CALCIPOTRIOL COMBINATIONS

BEFORE TREATMENT

22 WEEKS AFTER TREATMENT

Image No. 10 SIDE EFFECT

DIFFUSE ERYTHEMA DUE TO PUVA THERAPY

ERYTHEMA DUE TO CALCIPOTRIOL COMBINATIONS

DISCUSSION

In our study on the treatment of palmoplantar psoriasis with topical PUVA therapy and sequential treatment with topical calcipotriol and clobetasol ointment, the mean age of the patients presented with palmoplantar psoriasis was 43.32 year. 68% of patients were males and 32% were females and the mean duration of the disease was 17 months. Response to treatment were assessed based on reduction in PASI score and its percentage at 8^{th}, $16^{th}$and 24^{th} week.

TOPICAL PUVA (GROUP A)

The starting dose of UVA therapy was $1J/cm^2$ with an increment of $0.5\ J/cm^2$ on subsequent visit. The maximum dose reached was 24.5 J/cm2 for some patients. In our study, the group A patients treated with 8 methoxypsoralen solution along with ultraviolet A therapy twice weekly showed reduction in PASI score of 21.28%, 40.66%, 60.50% at the end of 8^{th}, $16^{th}$and 24^{th} respectively. Maximum improvement was observed at 24^{th} week.

There are many studies in literature about the topical PUVA in the treatment of palmoplantar psoriasis, but the results were not consistent. Various studies conducted for the treatment of palmoplantar psoriasis are

1. Wilkinson JD Ralfs IG et al, in this study 67% of patients showed considerable improvement with topical application of methoxypsoralen along with UVA [75].

2. Abel EA et al, in this study five (35.7%) out of 14 patients had complete clearance of lesions after 15 to 40 treatments [76].

3. Norbert J. Neumann et al, showed 64.64% reduction of PASI score[86].

4. Tsankov N et al, this study showed 40% of patients had marked improvement after 15 sessions of PUVA therapy [84].

5. **Petty A et al,** reported the most commonly used therapeutic options for palmo-plantar psoriasis are long-term treatment with topical corticosteroids and hand foot PUVA, but the disease become resistant to these modalities after sometime [85] .

6. Tsankov N et al, showed no statistically significant difference between the combination of calcipotriol with UVA phototherapy and PUVA in regard to the therapeutic effect [84] .

In our study for the treatment of palmoplantar psoriasis with PUVA therapy, 4 out of 22 patients (18.18%) had complete clearance of palmar psoriasis and 2 patients (9.09%) had complete clearance of plantar

psoriasis after 34 to 44 treatment sessions. 18 % of patients developed adverse effect during treatment. In the follow up period, 3 patients developed relapse after 15 weeks of remission. These findings in our study are comparable to the above mentioned studies conducted for the treatment of palmoplantar psoriasis with PUVA therapy.

The disadvantages of PUVA are unavailability of PUVA chamber in many centers, repeated hospital visits and long term side effects.

COMBINATION OF CALCIPOTRIOL WITH CLOBETASOL PROPIONATE OINTMENT (GROUP B)

The topical calcipotriol and clobetasol propionate ointment was given in a sequential manner for 6 months. In this group maximum percentage reduction of PASI score was 29.55%, 50.56% and 70.77% at the end of 8^{th}, 16^{th} and 24^{th} weeks respectively. The maximum improvement was observed at the end of 16^{th} and 24^{th} weeks.

Studies related to the treatment of palmoplantar psoriasis with combination of topical calcipotriol and steroids were very less but many studies were done with combination of calcipotriol and steroids for the treatment of other type of psoriasis.

These combinations showed better results for the treatment of localized plaque type of psoriasis. Eventhough the onset of action of

calcipotriol is slow; steroid will trigger its action and reduces the irritant potential of calcipotriol. The advantage of calcipotriol is that it can be given safely for children, diabetic and hypertensive patients.

In a randomized, double-blind controlled trial of **van der Vleuten CJ et al** [79] , 71.2% of patients achieved "absent" or "very mild" disease with the two-compound scalp formulation, compared to 64% with betamethasone dipropionate and 36.8% with calcipotriene alone. But the disadvantage is pruritus in the combination [79, 80].

The efficacy of occlusive topical calcipotriol therapy is better than nonocclusive therapy. The study by **Duweb et al,** showed better efficacy with occlusive calcipotriol applied for 6 weeks, twice-weekly occlusive calcipotriol ointment was as effective as the twice-daily application [81].

A study by **Lebwohl M** and **Menter A et al** , revealed that a high-potency topical corticosteroid in combination with vitamin D analog gave better efficacy, although it does not appear to be as effective as super potent corticosteroid used alone [82,83]. A combination with super potent topical clobetasol or halobetasol gave better results than with high potent topical betamethasone ointment.

In a similar study by **Koo J, Blum RR** and **Lebwohl M (2006) et al** with the combination of topical calcipotriol with clobetasol, there was a 92% clearance of skin lesions after 6 months of therapy [37].

In our study 16 patients (66.7%) showed more than 70% clearance of psoriatic skin lesions of both palms and soles after 6 months of therapy with topical calcipotriol and clobetasol with least side effects compared with 3 patients (13.6%) in PUVA therapy group.

In group B Seven patients (29.16%) showed 100% clearance of palmar psoriasis and five patients (20.83%) showed 100% clearance of plantar psoriasis after six months of therapy, which is comparable with the study done by **Koo J, Blum RR,Lebwohl M (2006) et al** .

CONCLUSION

1. Efficacy of topical calcipotriol ointment and steroid used in sequential manner is better than the topical psoralen ultraviolet A therapy.
2. All the patients (100%) in calcipotriol and steroid combination group showed more than 50% reduction of PASI score . But in PUVA therapy group 90% of patients showed more than 50% reduction of PASI score.
3. On comparing the adverse effects , patients on PUVA therapy group developed more adverse effects than the patients on calcipotriol and steroid combination group .
4. The duration of remission maintenance was long in calcipotriol and steroid combination group when compared to PUVA therapy group.

In our study, we arrived at the conclusion that topical therapies used in a sequential manner was more effective and it may be considered as a first line therapy for the treatment of patients with palmoplantar psoriasis.

PROFORMA FOR PALMOPLANTAR PSORIASIS

TITLE OF THE STUDY : Comparative study of efficacy of hand foot psoralen ultraviolet A therapy versus sequential therapy of topical clobetasol propionate with topical calcipotriol ointment in palmoplantar psoriasis

NAME:

AGE/SEX:

DATE:

OCCUPATION:

ADDRESS:

PHONE NO:

PRESENT HISTORY:

a) DURATION :

b) SYMPTOMS :

PAST HISTORY:

TREATMENT HISTORY:

FAMILY HISTORY:

GENERAL EXAMINATION:

BP : PR : FOCAL INFECTIONS :

SYSTEMIC EXAMINATION :

CVS : RS:

INVESTIGATIONS :

CBC : RFT :

RBS : LFT :

SERUM ELECTROLYTES :

BIOPSY :

FOLLOW UP : (PASI SCORE)

BEFORE TREATMENT 8WEEKS 16 WEEKS 24WEEKS

PASI PERCENTAGE REDUCTION :

8 WEEKS 16 WEEKS 24 WEEKS

SIDE EFFECTS :

ERYTHEMA/IRRITATION : OTHERS :

CONSENT FORM

Yourself Mr./Mrs./Ms…….. are being asked to be a participant in the research study titled ““ Comparative study of efficacy of hand foot psoralen ultraviolet A therapy versus sequential therapy of topical clobetasol propionate with topical calcipotriol ointment in palmo plantar psoriasis ””in CMC Hospital, Coimbatore, conducted by Dr.P.ABIRAMI, Post Graduate Student, Department of Dermatology, Venerology and Leprosy, Coimbatore Medical College Hospital. You are eligible after looking into the inclusion criteria. You can ask any question you may have before agreeing to participate.

Research Being Done

At Outpatient Department of Dermatology Coimbatore Medical College Hospital, Coimbatore.

Purpose of Research

To observe the efficacy and side effect of Psoralen ultra violet A therapy and combination treatment of topical clobetasol propionate with Calcipotriol ointment

Decline from Participation

You have the option to decline from participation in the study existing protocol for your condition.

Privacy and Confidentiality

Privacy of individuals will be respected and any information about you or provided by you during the study will be kept strictly confidential.

Authorization to publish Results

Results of the study may be published for scientific purposes and/or presented to scientific groups; however you will not be identified.

Statement of Consent

I volunteer and consent to participate in this study. I have read the consent or it has been read to me. The study has been fully explained to me in my own language, and I may ask questions at any time.

---------- ----------

Signature /Left thumb impression (Volunteer) Date

---------- ----------

Signature of witness Date

ABBREVIATIONS

IL	–	Interleukin
IFN	–	Interferon
ICAM	–	InterCellular Adheshion Molecule
TNF	–	Tumor Necrosis Factor
PASI	–	Psoriasis Area Severity Index
UVA	–	Ultraviolet A
FDA	–	Food and Drug Administration
RXR	–	Retinoid Receptor X [Rexinoid]
GM – CSF	–	Granulocyte Monocyte Colony Stimulating Factor
Th1, Th2	–	Helper T cell 1, 2
CD	–	Cluster Differentiation
TCS	–	Topical Corticosteroids
MOP	–	Methoxypsoralen
MA	–	Monoadducts
TMP	–	Trimethoxypsoralen
GIT	–	Gastrointestinal Tract
RePUVA	–	Retinoid with PUVA
P	–	Palmar
PL	–	Plantar
SD	_	Standard Deviation

MASTER CHART

S.NO	AGE (YRS)	SEX M/F	DURATION (MTH)	PASI SCORE (WKS)				PASI % RED (WKS)			AE	REMISSION (WKS)	RELAPSE (WKS)
				BT	8	16	24	8	16	24			
1	32	F	24	3.8	3	2.4	1.4	21.05	36.84	63.16	N		
2	36	M	7	3	2.6	1.8	1.2	13.33	40	60	N		
3	26	M	48	4	2.6	2	0.8	35	50	80	N	17(P)	
4	40	M	18	2.8	2.6	1.6	1.4	7.14	42.86	50	N		
5	47	M	9	4	2.8	2.2	1.6	30	45	60	N		
6	59	M	8	2.6	2	1.6	0.8	23.08	38.46	69.23	N	16(P)	
7	64	M	30	4.4	3.8	2.8	2.2	13.64	36.36	50	N		
8	39	M	9	1	0.6	0.4	0.2	40	60	80	Y	22(PL)	20(PL)
9	67	M	12	3	1.8	1.6	0.8	40	46.67	73.33	N	20(P)	
10	19	M	18	1.8	1.2	0.8	0.6	33.33	55.56	66.67	N		
11	55	M	7	2.4	1.8	1.2	0.8	25	50	66.67	Y	18(P)	13(P)
12	38	M	9	3.8	-	-	-	-	-	-	N		
13	50	M	9	3.6	3	2.8	2	16.67	22.22	44.44	N		
14	28	F	7	1.8	1.6	1.4	0.6	11.11	22.22	66.67	N	21(PL)	12(PL)
15	54	M	6	3.6	3	2.4	1.6	16.67	33.33	55.56	Y		
16	42	M	11	2.4	1.8	1.2	1	25	50	58.33	N		
17	60	F	36	4.4	3.6	3	2	18.18	31.82	54.55	N		
18	20	M	24	6	4.8	3.6	2.2	20	40	63.33	N		
19	53	M	6	3.8	3.2	3	1.8	15.79	21.05	52.63	N		
20	30	M	36	5	4.2	3.2	2.4	16	36	52	N		
21	62	F	7	3.2	-	-	-	-	-	-	N		
22	46	M	12	3.6	3	3.6	1.6	16.67	50	55.56	N		
23	70	M	30	3.8	3.4	3.8	2.2	10.53	26.32	42.11	Y		

KEY TO MASTER CHART

1 - 25	-	GROUP A
26 – 50	-	GROUP B
12, 21, 24, 48	–	LOST FOLLOW UP
YRS	–	YEARS
M/F	–	MALE/FEMALE
MTH	–	MONTHS
PASI	–	PSORIASIS AREA SEVERITY INDEX
WKS	–	WEEKS
BT	–	BEFORE TREATMENT
RED	–	REDUCTION
AE	–	ADVERSE EFFECTS
N	–	NO
Y	–	YES
P	–	PALMAR
PL	–	PLANTAR

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